

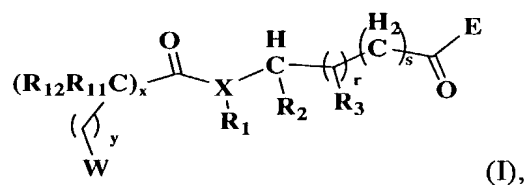
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CLAIMS

We claim:

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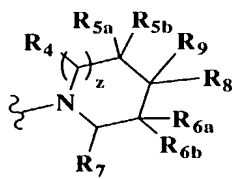
1. A compound according to formula (I),



10

or a pharmaceutically-acceptable salt, hydrate or prodrug thereof,

in which



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E is ;

X is N or CH;

R₁ is hydrogen or C₁₋₆alkyl or is taken together with R₂ or R₃ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R₂ is hydrogen, aryl, cycloalkyl, heteroaryl, heterocyclo; or C₁₋₆alkyl or C₂₋₆alkenyl

20

optionally substituted with one to three of hydroxy, alkoxy, halogen, cyano, nitro, trifluoromethyl, amino, alkylamino, aryl, cycloalkyl, heteroaryl, and/or heterocyclo; or R₂ is taken together with R₁ or R₃ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R₃ is hydrogen or C₁₋₆alkyl or is taken together with R₁ or R₂ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

25

R₄, R₅, R_{5a}, R_{5b}, R₆, R_{6a}, R_{6b}, and R₇ are independently selected from hydrogen, alkyl, substituted alkyl, halogen, hydroxy, alkoxy, keto, aryl, heteroaryl, cycloalkyl, and

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heterocyclo, or R_{5a} and/or R_{5b} , R_{6a} and/or R_{6b} , are taken together with R_8 or R_9 to form a fused carbocyclic, heterocyclic or heteroaryl ring;

R_8 and R_9 are independently hydrogen, halogen, cyano, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclo, aryl, heteroaryl, $-OR_{13}$, $-NR_{13}R_{14}$, $-SR_{13}$

5 $-S(O)_pR_{14}$, $-C(=O)R_{13}$, $-OC(=O)R_{13}$, $-CO_2R_{13}$, $-C(=O)NR_{13}R_{14}$, $-NR_{13}C(=O)R_{14}$, $-OC(=O)NR_{13}R_{14}$, $-NR_{13}CO_2R_{14}$, $-NR_{13}C(=O)NR_{14}R_{15}$ or $-NR_{13}SO_2R_{14}$; or R_8 and R_9 taken together form a monocyclic or bicyclic cycloalkyl or heterocyclo joined in a spiro fashion to ring E at C^* , provided that R_8 and R_9 are not both hydrogen, and provided further that when R_8 is $-OR_{13}$, $-(CH_2)_k$ -aryl or $-(CH_2)_k$ -heteroaryl, 10 then R_9 is not $-C(=O)NR_{18}R_{19}$, $-CO_2R_{19}$, $-(CH_2)_mNR_{18}SO_2R_{20}$, $-(CH_2)_mNR_{18}C(=O)R_{20}$, $-(CH_2)_mOR_{19}$, $-(CH_2)_mO(C=O)R_{20}$, $-CH(R_{18})R_{19}$, or $-(CH_2)_mNR_{18}(C=O)NR_{19}R_{21}$;

R_{11} and R_{12} are selected independently of each other from hydrogen, alkyl, halogen, hydroxy, hydroxyalkyl, haloalkyl, amino, aminoalkyl, alkylamino, arylalkyl, 15 cycloalkylalkyl, heteroarylalkyl, aryl, and cycloalkyl, and where y is at least 1, then R_{11} and R_{12} may be heterocyclo or heterocycloalkyl, or R_{11} and R_{12} , when attached to the same carbon atom, may join to form a spirocycloalkyl ring;

R_{13} , R_{14} and R_{15} are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heterocyclo, or heteroaryl; or R_{13} and R_{14} , or R_{14} and R_{15} may join together to 20 form a heterocyclo or heteroaryl, except R_{14} is not hydrogen when joined to a sulfonyl group as in $-S(O)_pR_{14}$ or $-NR_{13}SO_2R_{14}$;

W is selected from:

2) $-NR_{16}R_{17}$, $-NR_{16}C(=O)R_{22}$, $-NR_{16}CO_2R_{22}$, $-OR_{23}$, amidino, and guanidino;
 2) heteroaryl or heterocyclo groups selected from pyrrolyl, furyl, thienyl, 25 imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, 3-azaisothiazolyl, pyridyl, pyrazinyl, pyridazinyl, 1,2-dihydropyridazinyl, and pyranyl, wherein said heteroaryl and heterocyclo groups may be substituted or unsubstituted and may have an optionally-substituted carbocyclic, heterocyclic or heteraryl ring fused thereto; or

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R_{26} is hydrogen, alkyl, substituted alkyl, aryl, heterocyclo, cycloalkyl, or heteroaryl,
except when joined to a sulphonyl group as in SO_2R_{26} , then R_{26} is not hydrogen;

k and m are independently 0, 1, 2 or 3;

p is 1, 2, or 3;

5 r is 0 or 1;

s is 0 or 1;

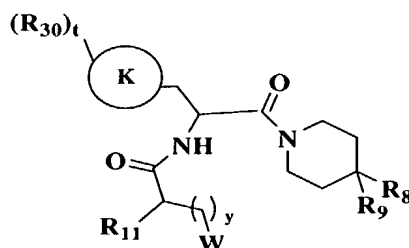
u and v are 0, 1, 2, or 3;

w is 0, 1, or 2;

x and y are 0, 1, 2, 3, or 4; and

10 z is 0, 1, or 2.

2. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, having the formula:



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in which,

K is aryl or heteroaryl;

R_{30} is attached to any available carbon or nitrogen atom of K and is selected from C_1 -

20 alkyl, hydroxy, alkoxy, halogen, nitro, cyano, amino, alkylamino, phenyl, and –
 $C(=O)$ phenyl; and

t is 0, 1 or 2.

3. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate,
25 or prodrug thereof, in which

W is $-NR_{16}R_{17}$, $-NHC(=O)R_{22}$, $-NHCO_2$ alkyl, OR_{23} , or azetidiny;

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- R_{16} and R_{17} are independently selected from hydrogen, C_{1-8} alkyl, and $(CH_2)_q$ -J, wherein J is selected from naphthyl, furanyl, indolyl, imidazolyl, pyrimidinyl, benzothienyl, pyridinyl, pyrrolyl, pyrrolidinyl, thienyl, and C_{3-7} cycloalkyl, wherein the alkyl, alkylene, and/or J groups of R_{16} and/or R_{17} are optionally substituted with up to three R_{32} ;
- R_{22} is selected from C_{1-6} alkyl, trifluoromethyl, alkoxyalkyl, furylalkyl, alkylaminoethyl, phenyl, pyrrolylalkyl, piperidinyl, and piperidinylalkyl, wherein R_{22} in turn is optionally substituted with one to two C_{1-4} alkyl and/or $-CO_2(C_{1-4}alkyl)$;
- R_{23} is hydrogen or phenyl;
- R_{32} is selected from C_{1-6} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, amino C_{1-4} alkyl, trifluoromethyl, halogen, phenyl, benzyl, phenyloxy, benzyloxy, $-C(=O)(CH_2)NH_2$, $-CO_2(C_{1-4}alkyl)$, $-SO_2(C_{1-4}alkyl)$, tetrazolyl, piperidinyl, pyridinyl, and indolyl, wherein when R_{32} is a ring, said ring in turn is optionally substituted with one to two C_{1-4} alkyl, hydroxy, methoxy, and/or halogen; and
- q is 0, 1, 2 or 3.
4. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which

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4alkoxy, hydroxyC₁₋₄alkyl, -C(=O)alkyl, -C(=O)aminoalkyl, -C(=O)phenyl,
 -C(=O)benzyl, -CO₂alkyl, -CO₂phenyl, -CO₂benzyl, -SO₂alkyl,
 -SO₂aminoalkyl, -SO₂phenyl, -SO₂benzyl, phenyl, benzyl, phenoxy,
 benzyloxy, pyrrolyl, pyrazolyl, piperidinyl, pyridinyl, pyrimidinyl, and tetrazolyl,
 5 and/or two R₂₅ when attached to adjacent carbon atoms may be taken together to
 form a fused benzo or pyrazolyl ring, and/or two R₂₅ when attached to the same
 carbon atom (in the case of a non-aromatic ring) may form keto (=O), and each
 R₂₅ in turn is optionally substituted with up to two R₃₁;

R₃₁ is selected from halogen, trifluoromethyl, C₁₋₄alkyl, hydroxy, and C₁₋₄alkoxy;
 10 w is selected from 0, 1, or 2; and
 u and v are selected from 0, 1, and 2.

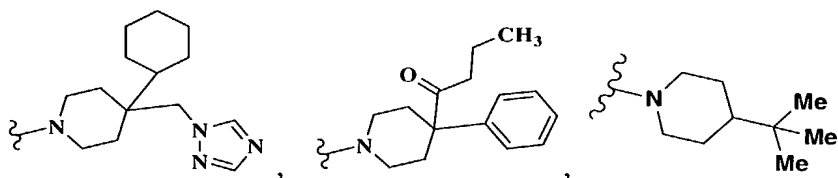
5. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate,
 or prodrug thereof, in which
 15 R₈ and R₉ are selected independently from hydrogen, alkyl, -(CH₂)_j-C(=O)alkyl, -(CH₂)_j-
 phenyl, -(CH₂)_j-naphthyl, -(CH₂)_j-C₄₋₇cycloalkyl, -(CH₂)_j-heterocyclo, and -
 (CH₂)_j-heteroaryl, or R₈ and R₉ together form a spirocycloalkyl or
 spiroheterocyclic ring; and
 j is selected from 0, 1, 2 and 3.

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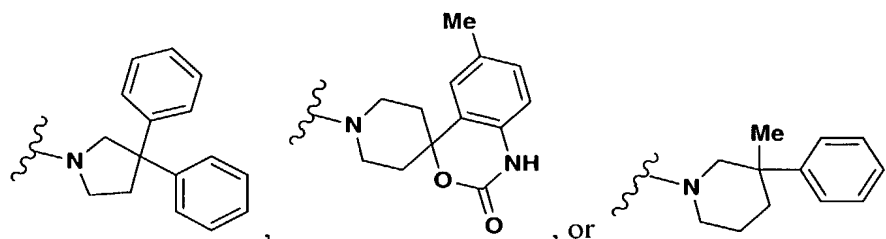
6. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate,
 or prodrug thereof, in which

E is

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5 7. A compound according to claim 1, or a pharmaceutically-acceptable salt thereof, in which

R_{11} and R_{12} are (i) at each occasion independently selected from:

- a) hydrogen,
- b) C_{1-6} alkyl,
- 10 c) C_{1-6} alkyl substituted with up to two of hydroxy, alkoxy, amino, alkylamino, imidazolyl, pyrazolyl, phenyl, naphthyl, pyridinyl, indolyl, pyrimidyl, furyl, thiazolyl, and thienyl, wherein said ringed substituents in turn are optionally substituted with one to three R_{33} and/or have a benzene ring fused thereto optionally substituted with one to two R_{33} ;
- 15 d) C_{3-7} cycloalkyl optionally substituted with up to two R_{33} and/or having a benzene ring fused thereto, wherein said fused benzene ring is optionally substituted with up to two R_{33} ;
- e) phenyl optionally substituted with up to three R_{33} ;
- f) where y is at least one, R_{11} and R_{12} may also be selected from piperidinyl, pyrrolidinyl, piperidinylalkyl, and pyrrolidinylalkyl, in turn optionally substituted with up to three R_{33} ; or
- 20

ii) alternatively, one of R_{11} and one of R_{12} attached to the same carbon atom may be taken together to form a spirocycloalkyl ring;

R_{33} is selected from C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halogen, nitro, phenyl, benzyl, phenyloxy, benzyloxy, $-C(=O)$ phenyl, amino, alkylamino, and aminoalkyl, wherein when R_{33} includes a phenyl group said phenyl group in turn is

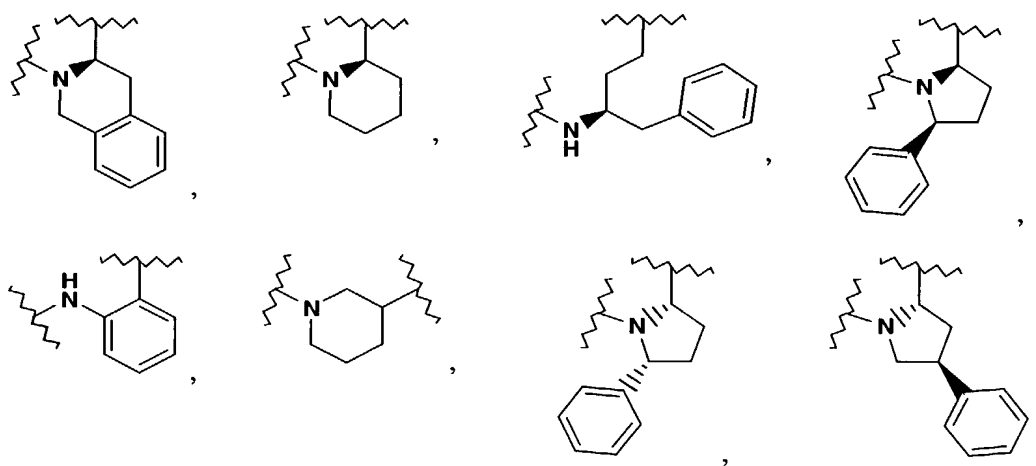
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optionally substituted with one to two of halogen, nitro, cyano, C₁₋₄ alkyl, and/or C₁₋₄ alkoxy.

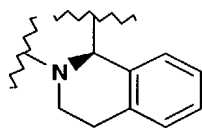
- 5 8. A compound according to claim 1, or a pharmaceutically-acceptable salt thereof, in which
- R₂ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, biphenyl, C₂₋₆alkenylene-K, and – (CH₂)_g-K;
- K is selected from phenyl, naphthyl, thienyl, thiazolyl, pyridinyl, pyrimidinyl, and C₅₋₆cycloalkyl, wherein each group K in turn is optionally substituted with one to three R₃₀ or has a benzene ring fused thereto, which also may be substituted with one to three R₃₀;
- 10 R₃₀ is selected from C₁₋₄alkyl, hydroxy, alkoxy, halogen, nitro, cyano, amino, alkylamino, phenyl, and acylphenyl; and
- 15 g is 0, 1, 2 or 3.

9. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which -X(R₁)-CH(R₂)-CH(R₃)_r-(CH₂)_s-, taken together are selected
- 20 from C₁₋₄alkylene,

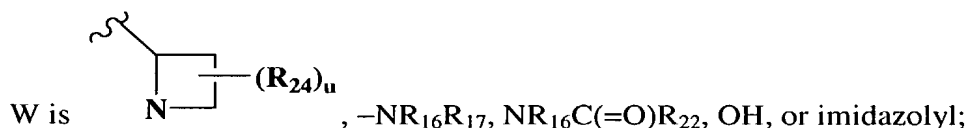


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and



10. A compound according to claim 1, or a pharmaceutically-acceptable salt thereof, in which
- 5 X is N;
 R_1 is hydrogen or C_{1-4} alkyl;
 r is 0; and
 s is 0.
- 10 11. A compound according to claim 10, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which



- R_{16} and R_{17} are selected from hydrogen and C_{1-4} alkyl;
 R_{22} is C_{1-4} alkyl, phenyl or piperidinyl C_{1-4} alkyl;
 15 R_{24} is C_{1-4} alkyl; and
 u is 0 or 1.

12. A compound according to claim 11, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which
- 20 R_{11} is hydrogen, C_{1-4} alkyl, or imidazolyl C_{1-4} alkyl; and
 R_{12} is hydrogen or C_{1-4} alkyl.

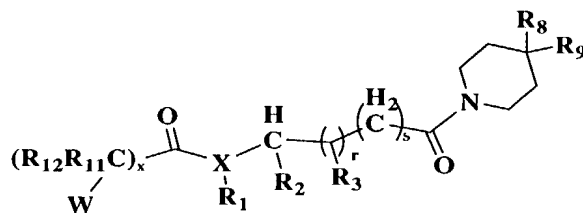
13. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which R_{16} and R_{17} are independently selected from hydrogen, C_1 -

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alkyl, and C₁₋₈substituted alkyl, except R₁₆ and R₁₇ are not alkyl substituted with pyridyl, imidazolyl, thiazolyl, pyrimidinyl, or piperazinyl, and W is not morpholinyl.

14. A compound according to the formula,

5



or a pharmaceutically-acceptable salt, hydrate or prodrug thereof,

10 in which

X is N or CH;

R₁ is hydrogen or C₁₋₆alkyl or is taken together with R₂ or R₃ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

15 R₂ is hydrogen, aryl, cycloalkyl, heteroaryl, or heterocycle; or a C₁₋₆alkyl or C₂₋₆alkenyl optionally substituted with one to three of hydroxy, halogen, aryl, cycloalkyl, heteroaryl, and/or heterocycle; or R₂ is taken together with R₁ or R₃ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

20 R₃ is hydrogen or C₁₋₆alkyl or is taken together with R₁ or R₂ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R₈ and R₉ are independently hydrogen, halogen, cyano, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -OR₁₃, -NR₁₃R₁₄, -SR₁₃, -S(O)_pR₁₄, -C(=O)R₁₃, -OC(=O)R₁₃, -CO₂R₁₃, -C(=O)NR₁₃R₁₄, -NR₁₃C(=O)R₁₄, -OC(=O)NR₁₃R₁₄, -NR₁₃CO₂R₁₄, -NR₁₃C(=O)NR₁₄R₁₅ or -NR₁₃SO₂R₁₄; or R₈ and R₉ taken together form a monocyclic or bicyclic cycloalkyl or heterocycle joined in a spiro fashion to ring E at C*;

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R₁₁ and R₁₂ are selected independently of each other from hydrogen, alkyl, halogen, hydroxy, hydroxyalkyl, haloalkyl, amino, aminoalkyl, alkylamino, arylalkyl,

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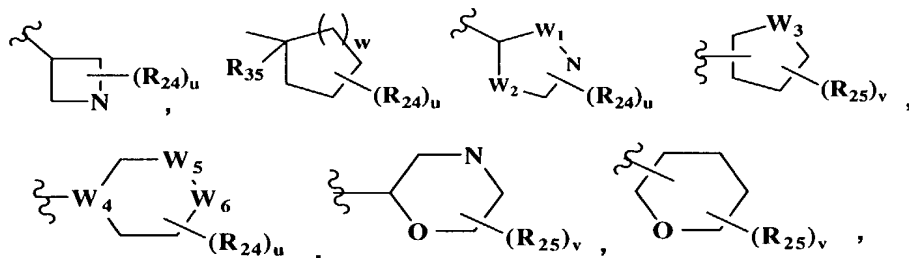
cycloalkylalkyl, heteroarylalkyl, aryl, and cycloalkyl, or R_{11} and R_{12} , when attached to the same carbon atom, may join to form a spirocycloalkyl ring; R_{13} , R_{14} and R_{15} are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heterocyclo, or heteroaryl; or R_{13} and R_{14} , or R_{14} and R_{15} may join together to form a heterocyclo or heteroaryl, except R_{14} is not hydrogen when joined to a sulfonfyl group as in $-S(O)_pR_{14}$ or $-NR_{13}SO_2R_{14}$;

W is selected from:

3) $-NR_{16}R_{17}$, $-NR_{16}C(=O)R_{22}$, $-NR_{16}CO_2R_{22}$, or $-OR_{23}$; or

4) heteroaryl or heterocyclo groups selected from pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, 3-azaisothiazolyl, pyridyl, pyrazinyl, pyridazinyl, 1,2-dihydropyridazinyl, and pyranyl, wherein said heteroaryl and heterocyclo groups may be optionally substituted with one to three R_{36} , and may have an optionally-substituted carbocyclic, heterocyclic or heteraryl ring fused thereto; or

3) a carbocyclic, heterocyclic, or heteroaryl ring selected from:



in which W_1 and W_2 are NH, CH_2 , O or S, W_3 is O or S, W_4 is N or CH , and W_5 and W_6 are NH or CH_2 , wherein when W_1 , W_2 , W_5 and W_6 are NH or CH_2 , said groups are optionally substituted with R_{24} ;

R_{16} and R_{17} are C_{1-8} alkyl or $(CH_2)_q$ -J, wherein J is selected from aryl, heteroaryl, heterocyclo, and cycloalkyl, wherein the alkyl, alkylene, and/or J groups of R_{16} and/or R_{17} are optionally substituted with up to three R_{32} ;

R_{22} is selected from C_{1-6} alkyl, trifluoromethyl, alkoxyalkyl, furylalkyl, alkylaminoethyl, phenyl, pyrrolylalkyl, piperidiny, and piperidinyalkyl, wherein R_{22} in turn is optionally substituted with one to two C_{1-4} alkyl and/or $-CO_2(C_{1-4}alkyl)$;

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R_{23} is hydrogen or aryl;

R_{24} and R_{25} at each occurrence are attached to any available carbon or nitrogen atom of W and at each occurrence are selected from hydrogen, C_{1-6} alkyl, halogen, substituted C_{1-6} alkyl, amino, alkylamino, $-C(=O)R_{26}$, $-CO_2R_{26}$, $-SO_2R_{26}$, $-OR_{26}$, aryl, heteroaryl, heterocyclo, and cycloalkyl, and/or two R_{25} attached to two adjacent carbon atoms or adjacent carbon and nitrogen atoms may be taken together to form a fused optionally-substituted heteroaryl, heterocyclo or cycloalkyl ring, and/or two R_{24} or two R_{25} when attached to the same carbon atom may form keto ($=O$);

R_{26} is hydrogen, alkyl, phenyl, benzyl, or aminoalkyl, except when joined to a sulphonyl group as in SO_2R_{26} , then R_{26} is not hydrogen;;

R_{32} is selected from C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halogen, nitro, phenyl, benzyl, phenyloxy, benzyloxy, $-C(=O)$ phenyl, amino, alkylamino, and aminoalkyl, wherein when R_{32} includes a phenyl group said phenyl group in turn is optionally substituted with one to two of halogen, nitro, cyano, C_{1-4} alkyl, and/or C_{1-4} alkoxy;

R_{35} and R_{36} at each occurrence is selected from C_{1-6} alkyl, halogen, substituted C_{1-6} alkyl, hydroxy, alkoxy, cyano, trifluoromethyl, trifluoromethoxy, nitro, acyl, carboxyalkyl, sulfonyl, aryl, heteroaryl, heterocyclo, and cycloalkyl;

p is 1, 2 and 3;

r is 0 or 1;

s is 0 or 1;

u and v are 0, 1, or 2;

w is 0, 1, or 2; and

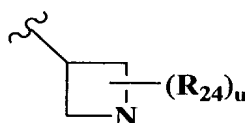
x is 0, 1, 2, 3, or 4.

15. A compound according to claim 14, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which

X is N;

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R_1 is hydrogen or C_{1-4} alkyl;

W is , $-NR_{16}R_{17}$, or $NR_{16}C(=O)R_{22}$;

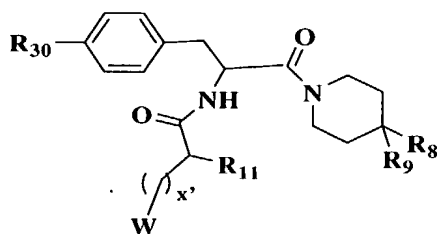
R_{24} is C_{1-4} alkyl;

r is 0;

5 s is 0; and

u is 0 or 1.

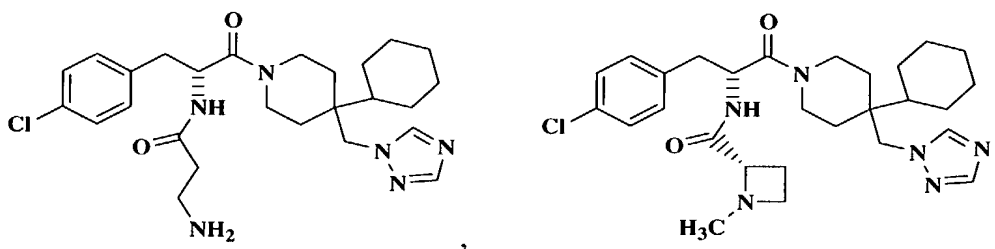
16. A compound according to claim 14, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, having the formula,



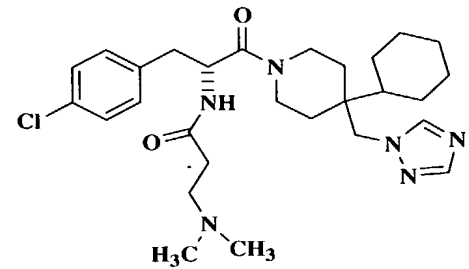
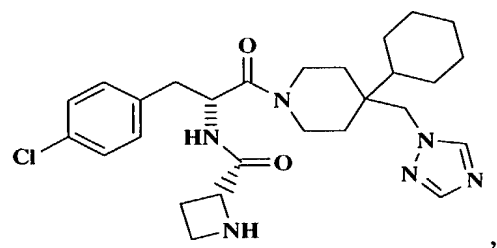
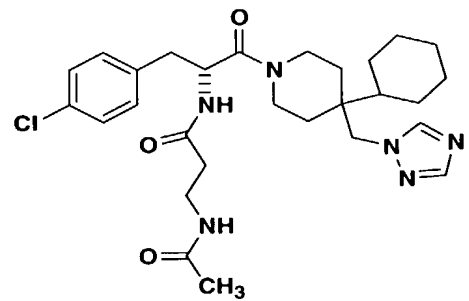
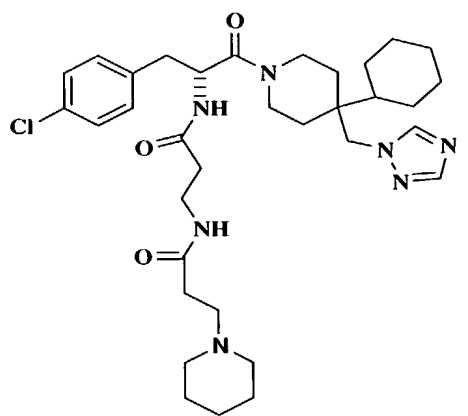
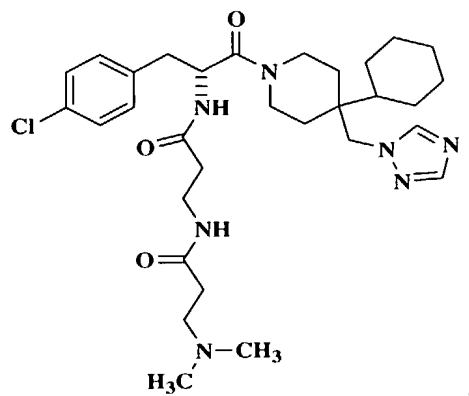
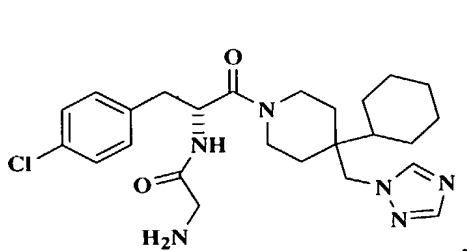
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in which x' is 0, 1 or 2 and R_{30} is halogen or methoxy.

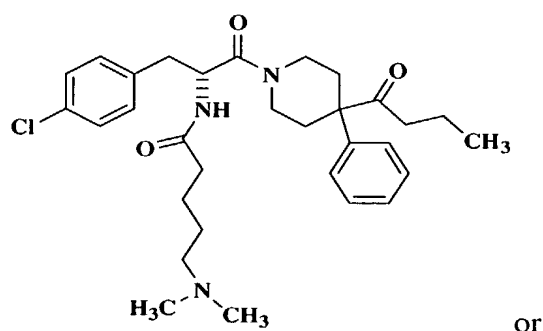
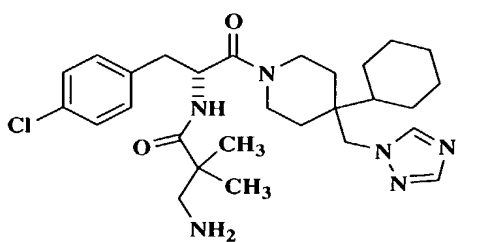
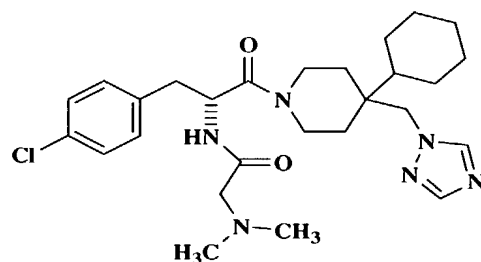
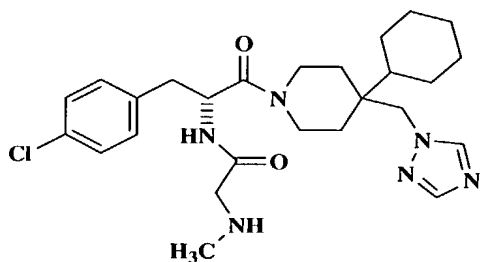
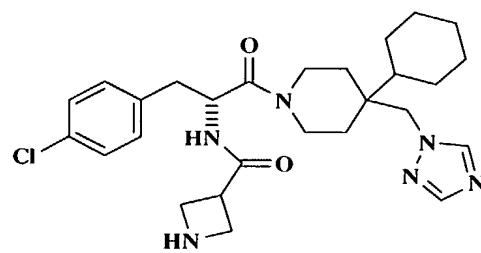
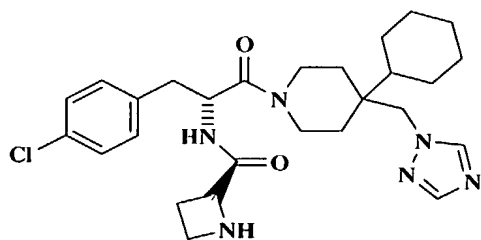
17. A compound according to claim 1, having the formula,



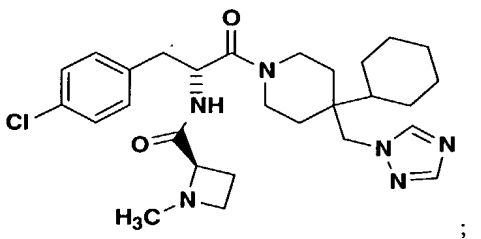
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or



or a pharmaceutically-acceptable salt, hydrate, or prodrug thereof.

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18. A pharmaceutical composition comprising at least one compound according to claim 1 or a pharmaceutically-acceptable salt hydrate, or prodrug thereof; and a pharmaceutically-acceptable carrier or diluent.

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19. A pharmaceutical composition comprising (i) at least one compound according to claim 1 or a pharmaceutically-acceptable salt hydrate, or prodrug thereof; (ii) at least one second compound effective for treating an inflammatory or immune disease, a cardiovascular disease, or neurodegenerative disorder; and (iii) a pharmaceutically-
10 acceptable carrier or diluent.

20. The pharmaceutical composition according to claim 19 in which the at least one second compound comprises a phosphodiesterase inhibitor.

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21. A method of treating a melanocortin-receptor associated condition, the method comprising administering to a warm-blooded species in need of such treatment a therapeutically-effective amount of at least one compound according to claim 1.

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22. The method of claim 21 in which the melanocortin-receptor associated condition is an MC-1R or MC-4R associated condition.